Review Article

Transcriptional Regulatory Network of Cis-Regulatory Elements (*Cres*) and Transcription Factors (Tfs) In Plants during Abiotic Stress

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Abstract

Changing environmental conditions are limiting crop productivity and, hence, there is an urgent need to develop stress tolerant plants. Engineering of *Cis*-regulatory elements (CREs) is an effective strategy to design such plants. Transcription factors (TFs) can be used effectively to manipulate gene expression. However, overlapping expression has been observed for several stress-responsive TFs. In order to design improved plants by *Cis*-engineering, we first need to understand the complex regulatory network of TFs and the cross-talk between them. Advances in systems biology have enabled us to visualize plants from a holistic view during the abiotic stress. The current review discusses major transcriptional regulatory networks involved in abiotic stress tolerance, and how a better understanding of these networks may help in designing stress-tolerant plants. Finally, the review mentions some potential approaches to generate stress-tolerant crops to enhance crop productivity, which is the ultimate goal of all plant genetic engineering studies.

ABBREVIATIONS

CREs- *Cis*-regulatory Elements; TFs- Transcription Factors; LEA- Late Embryogenesis Abundant; DREB- Dehydration Response Element Binding; AP2- Apetala 2; ERF- Ethylene Responsive Element Binding Factor; C2H2- Cys-2-His-2; ZF- Zinc Finger; MYB- Myeloblastosis; bHLH- Basic Helix Loop Helix; bZIP- Basic Leucine Zipper; NAC- NAM, ATAF1/2, CUC2; NAM- No Apical Meristem; ATAF1/2- *Arabidopsis* Transcription Activation Factor; CUC2- Cup-Shaped Cotyledon; PBM- Protein Binding Microarray; RLK- Receptor Like Kinase; HK- Histidine Kinase; InsP- Inositol Phosphate; ROS- Reactive Oxygen Species; ABA- Abs*Cis*ic acid; DRE/CRT- Dehydration Response Element/C-repeat; MYC- Myelocytomatosis; MYCR- MYC Recognition; MYBR- MYB Recognition; ABRE- Abs*Cis*ic Acid Response Element; NACR- NAC Recognition; CE- Coupling Element; AREB/ABF- ABRE Binding Protein; SnRK- SNF (Sucrose non-fermentable) Related Kinase; *rd22*- Dehydration Responsive 22; SNAC- Stress Responsive NAC; HMG- High Mobility Group; EREBP- Ethylene Responsive Element Binding Protein; ARFs- Auxin Response Factors; IAA- Indole Acetic Acid; PlnTFDB- Plant TF Database; STIFDB- Stress Response TF Database; TRAB1- Transcription Factor Responsible For ABA Regulation 1; ABI- ABA Insensitive; RAV- Related to ABI3/VP1; VP- Viviparous; PR- Pathogenesis Related; BTERF- Benzothiadiazole Induced ERF2; CaPF1- *Capsicum annum* Pathogen And Freezing Tolerance Related Protein; HSF- Heat Shock Factors; TPS5- Trehalose Phosphate Synthase5

INTRODUCTION

Meeting the food requirements of the constantly growing population is becoming a challenge with reducing cultivable land and unpredictable climate changes. In nature, plants are exposed to both biotic as well as abiotic stresses which limit their growth and productivity. It is considered that every 1 degree rise in temperature results in 6% decrease in wheat production [1]. Various approaches has been utilized like traditional plant breeding and modern genetic engineering techniques to produce plants with high yields and which are more adaptable to changing environmental conditions, but each approach having its own constraints. So it is a pre-requisition to look for alternative strategies. One such strategy is to design plants by modulating, the regulatory regions of the stress inducible genes such as *Cis*-regulatory elements (CREs) located upstream of the gene that act as binding site for various transcription factors. Hence, designing of promoters by engineering of *Cis*-regulatory elements (CREs) has opened up new avenues for crop improvement [2].

Many stress inducible genes have been identified in plants

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[3-6] and the products of these genes not only provide stress tolerance but also regulate the expression of other genes and signal transduction pathways under stress conditions [7-9].

STRESS–RESPONSIVE GENES PRODUCTS ARE BROADLY CLASSIFIED INTO WO GROUPS

The products of the stress inducible genes can be broadly categorized in two groups (Figure 1): a) Stress tolerance proteins and b) Regulatory proteins. Chaperones, osmotin, LEA (late embryogenesis abundant) proteins, mRNA-binding proteins, antifreeze proteins, key enzymes for osmolyte biosynthesis (proline), water channel proteins, transporters (sugar and proline), detoxification enzymes, enzymes involved in fatty acid metabolism, inhibitors of proteinase, ferritin, and proteins which transfer lipid, ROS and RNS (reactive nitrogen species) produced in response to abiotic stresses [10-12] fall under the category of stress tolerance proteins. While regulatory proteins include transcription factors (TFs), kinases and phosphatases, which are involved in the regulation of gene expression and signal transduction pathways activated in response to stress [13-15].

ABSCISIC ACID (ABA) BIOSYNTHESIS IS INCREASASED DURING ABIOTIC STRESS

Plant development is affected at multiple stages by the stress and the level of effect relies on the timing and duration of the stress condition. Generally, a particular stress condition is followed by others stresses too e.g. drought, high salinity and low temperature stresses leads to osmotic stress. These stress conditions elicit complex responses [16,17] which results in changes at whole-plant, tissue, cellular, physiological and molecular levels. Increased biosynthesis of phytohormone abs*Cis*ic acids has been observed in plants under these stresses.

Increased levels of calcium has also been demonstrated in plants exposed to ABA, drought, cold and high salt stresses [7,17-19].

ABA-dependent and ABA-independent signaling pathways are involved in stress response

ABA performs various functions in plants such as seed dormancy, seed desiccation, guard cell opening-closing, abiotic stress tolerance, etc. [18,7,17,19].Whenever plants are exposed to certain abiotic stress viz. cold, salt, drought and biotic stress like wounding, they start synthesizing a phyohormone ABA in various organs in response to these stresses. This increased status of ABA acts as a regulator in various stress defensive processes like stomatal closure, expression of stress related genes. Closure of stomatal aperture leads to water reservation in plants. Plants reciprocate to stresses through triggering both ABA-dependent and ABA-independent processes [20]. Usually stomatal opening and closing is controlled by several environmental attributes viz. light, CO_2 level, abiotic and biotic stresses. One of an important factor in regulation of stomatal control includes guard cell turgor pressure which is governed by ionic fluxes mediated through anion and cation channels affixed to the guard cell membrane. ABA functions as a chemical messenger under abiotic and biotic stress that in turn results in stomatal closure via the activation and inactivation of ion channels through the activity of protein kinases and phosphatases. There are various transcription factors like DREB, MYC/MYB, AREB/ABF, and NAC that are associated with the ABA-dependent and ABA-independent pathways (Figure 2). These TFs binds to their cognate **Cis**-regulatory elements DRE/CRT, MYCR/MYBR, ABRE, NACR respectively located upstream of the stress-inducible genes [15,21-24]. A characteristic G-BOX like *Cis*-regulatory element
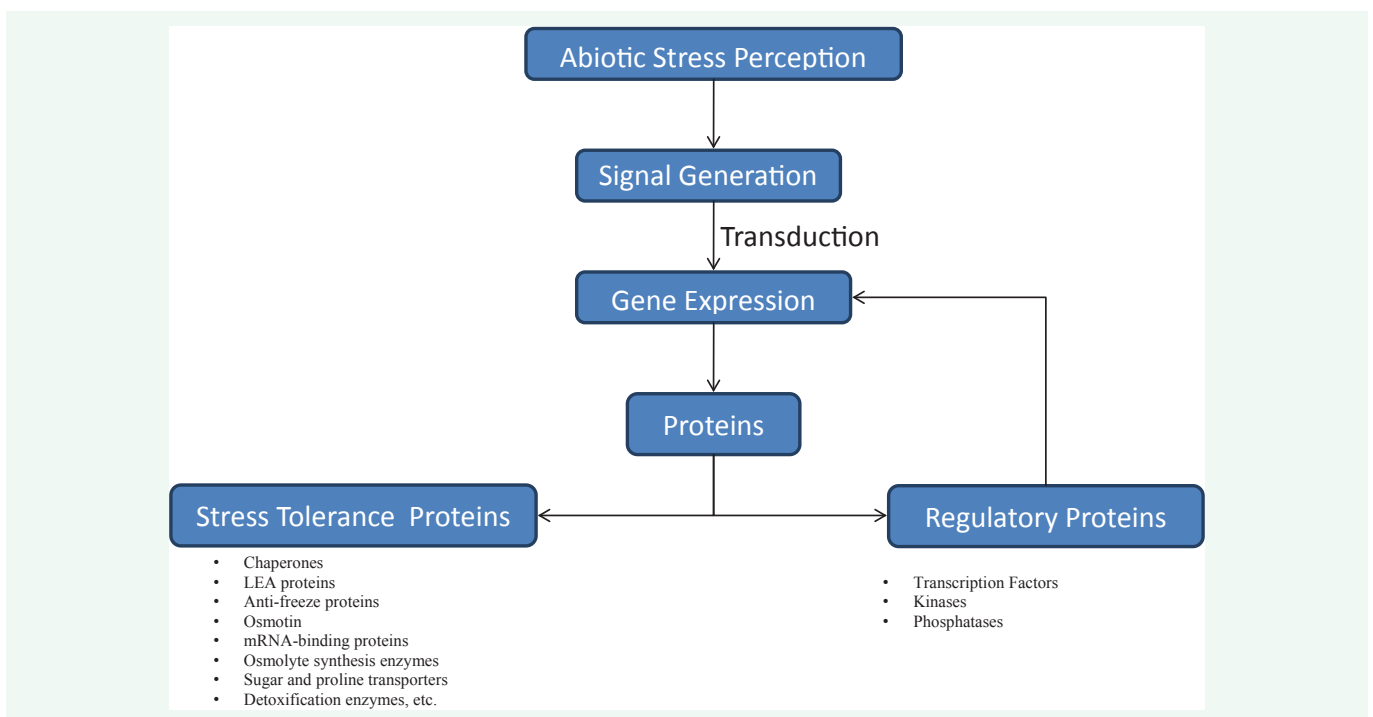

Figure 1 Classification of proteins produced in response to stress conditions.

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known as abs*Cis*ic acid responsive element (ABRE) (PyACGTGG/TC) is present in the upstream region of the ABA responsive genes [25]; this element is recognized by the members of the bZIP TF family known as AREB/ABF. The AREB/ABF undergoes phosphorylation by SnRK2s in the presence of ABA and then finally binds to ABRE elements to induce stress responsive genes [6] (Mehrotra *et al.* 2014). The MYB/MYC TFs bind to MYBR (CTAACCA) and MYCR (CACATG) elements respectively present in the promoter region of *rd22* gene (responsive to dehydration) and are thought to play role in stress responses as the synthesis of the MYB and MYC proteins was observed only once high levels of ABA has accumulated endogenously [18].

Components of ABA-dependent and ABA-independent signaling pathways cross-talk

Genetic analyses have stipulated that components associated with the ABA-dependent and ABA-independent signaling pathways often interact or eventually meet up with other components during the signaling pathway (Figure 2). The DREB1A/CBF3, DREB2A, and DREB2C proteins interact with AREB/ABF proteins [26]. The DREB2A gene for its expression under osmotic stress conditions requires an ABRE promoter sequence, AREB/ABF TFs, and SnRK2s, this suggest that complex interactions between the AREB and DREB regulons at the gene expression level as well as at protein level exists. AREB/ABFs

and NACs also interact at the gene expression level. In *A. thaliana*, the ABA biosynthetic gene NCED3 is directly regulated by the Stress responsive NAC (SNAC) TF ATAF1, suggesting the ABRE-dependent gene expression of ABRE regulons by SNAC TFs. On the other hand, ABRE sequences are present in the promoters of SNAC genes [27]. During dehydration and osmotic stress responses, *A. thaliana* ANAC096 interacts with AREB/ABF factors (ABF2/AREB1 and ABF4/AREB2). These results indicate that AREB/ABF and NAC regulons are inter-related. DREB/CBFs and other kinds of AP2/ERFs have also been observed to interact at the gene expression level. These observations arise a point that elements of the ABA-dependent and ABA–independent pathways cross-talk. *A. thaliana* ERF1 regulates gene expression by binding to two *Cis*-elements, the GCC box and DRE/CRT in response to different stress signals. ERF1 is an upstream TF in both ethylene and jasmonate signaling, and helps in resistance against pathogens. Results shows that under biotic stress conditions ERF1 binds to the GCC box (not the DRE/CRT) while under abiotic stress regulate expression by binding to DRE/CRT [28]; suggesting that ERF1 plays an important role in both biotic and abiotic stress responses by integrating ethylene, jasmonate and ABA signaling. In order to maximize the stress response these TFs may converse with each other. Tolerance against multiple stress can be achieved by the enhanced expression of ABA-dependent genes regulated by an over expressing TF [16] (Chinnusamy *et al.*
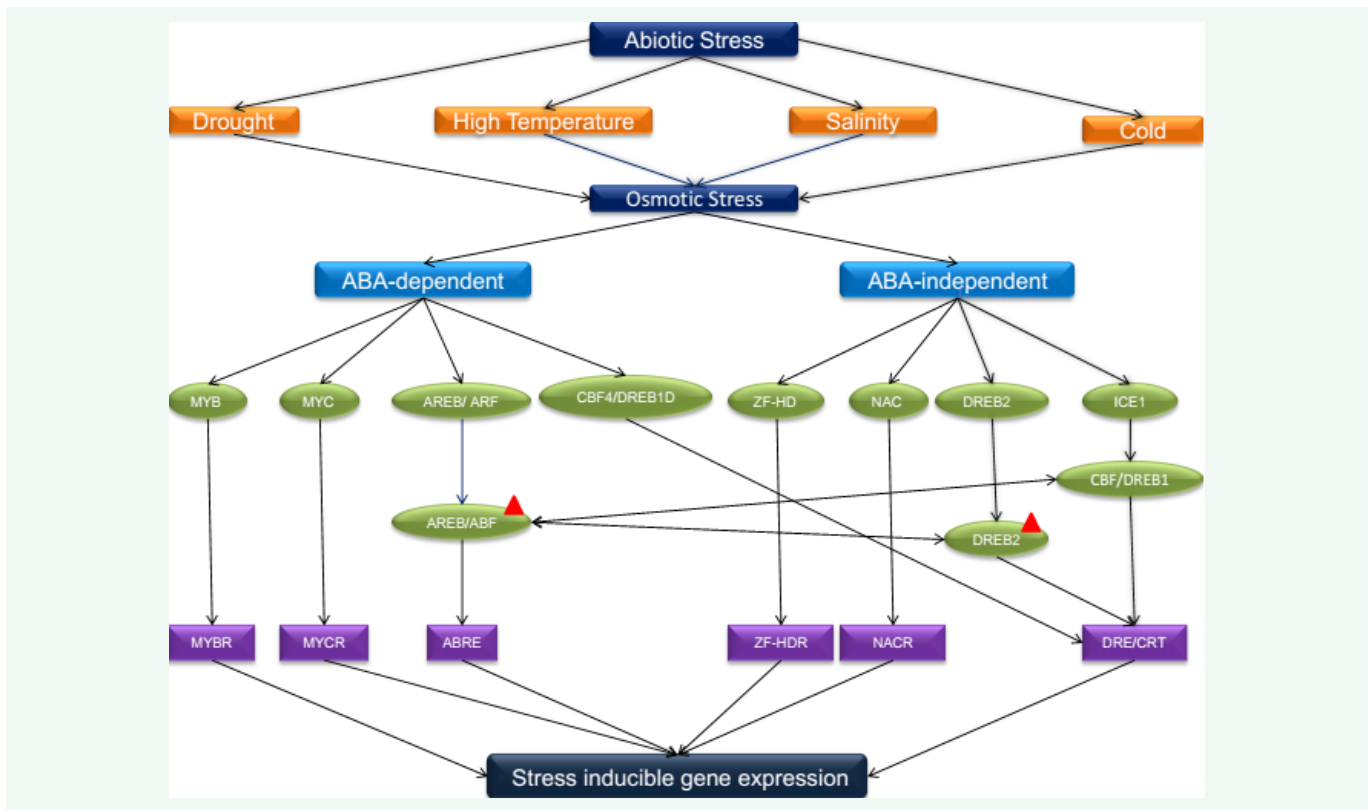
Figure 2 Transcriptional regulation activated in response to abiotic stress conditions. Transcriptional regulatory network involves interaction of *Cis*-regulatory elements (CREs) and transcription factors (TFs) involved in abiotic stress response. TFs controlling stress-inducible genes are shown in green ovals. Small red triangles depict modification of TFs in response to stress signals for their activation, such as phosphorylation. CREs involved in stress response is shown in purple rectangles. The double-headed arrow represents cross-talk between DREBs and AREB/ABFs based on the observation that DRE/CRTs act as a coupling element (CE) for ABRE. The ABA-independent DREB/CBF TFs bind to the DRE/CRT motif in the promoters of drought-responsive genes, and function as a coupling element for ABRE in ABA-dependent gene expression (Narusaka *et al.* 2003).

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2004). The drought-inducible expression of DREB1D is regulated by ABA-dependent pathways, indicating that DREB1D protein may function in the slow response to drought that depends on the accumulation of ABA. In transgenic *Arabidopsis* plants the expression of *erd1*gene observed to be induced in response to over-expression of both ZF-HD and NAC proteins under normal growth conditions (non-stressed) [29]. TFs like DREB2A and DREB2B Trans-activate the DRE *Cis*-element of osmotic stress genes and thereby are involved in maintaining the osmotic equilibrium in the cell [18]. Some genes like *rd22* lack the DRE/CRT elements in their promoter suggesting their regulation by some other mechanism.

A GREATDIVERSITY OF TRANSCRIPTION FACTORS ARE ACTIVATED DURING ABIOTIC STRESS

There are more than 1500 TFs in plants that are involved in regulation of the target genes at transcriptional level through complex signaling networks [30,31]. Approximately 6% of the plant (**Arabidopsis thaliana**) genome codes for TFs, the transcription factor gene content of plants are more as compared to *Drosophila*, *C. elegans*, and yeast which have approximately 4.6, 3.5, and 3.5% of their genes transcribing TFs respectively [30]. Under abiotic stress conditions, a large number of TFs gets activated which are involved not only in the transcriptional regulation but also play an important role in signal transduction pathways [15]. A study of the expression profile of around 7000 **Arabidopsis thaliana** genes under different stress conditions such as drought, cold and high-salinity was carried out [32]. The study corroborated that diverse transcription factor family genes are up regulated during abiotic stresses. The genes which were found to be upregulated were dehydration responsive element binding protein (DREB), APETALA 2/ethylene responsive element binding factor (AP2/ERF), Cys-2-His-2 (C2H2) type zinc finger (ZF) family, WRKY, myeloblastosis (MYB-R_2R_3), basic helix loop helix (bHLH), basic leucine zipper (bZIP) and NAC (NAM, ATAF1/2 and CUC2). The technical advances made in studying DNA-protein interactions have led to an enhanced understanding of preferences of TFs for particular sequence motifs [33-38]. Sometimes TFs prefer to bind to the flanking sequences in addition to the core sequence, of a particular motif [39].

TRANSCRIPTION FACTOR FAMILIES INVOLVED IN STRESS SIGNALING

TFs involved in stress signaling pathways can be categorized into different families depending on their conserved DNA binding domains or other functional modular structures (Riechmann *et al.* 2000) which includes basic helix–loop–helix (bHLH), basic leucine zipper (bZIP), zinc finger (ZF) and high-mobility group (HMG). The AP2/EREBP (apetala 2/ethylene responsive element-binding protein), NAC (NAM, ATAF, and CUC), and WRKY families, the trihelix DNA-binding factors, auxin response factors (ARFs), Aux/IAA factors (which interact with the ARF proteins and regulate gene expression) and other smaller families like DREB, AP2/ERF, bZIP, NAC (Table 1) are few transcription factor families that are present only in plants [30].

The PlnTFDB 3.0, for *A. thaliana* contains about 2451 distinct protein sequences of TFs and arranged them into 81 gene families (depicted in Figure 3) [40]. According to the Stress Responsive Transcription Factor Database (STIFDB V2.0) 3150 stress responsive genes are found to be present in the *A. thaliana*, 1118 stress responsive genes in *Oryza sativa* sub. *japonica* and 1716 stress responsive genes in O. *sativa* sub. *indica*, respectively (Figure 4-5). [41-43]. The gene density of stress responsive genes is highest on chromosome 3 in case of *A. thaliana* whereas in *Oryza sativa* sub. *japonica*and *Oryza sativa* sub. *indica*stress responsive gene density is highest on Chromosome 3 and Chromosome 1 respectively.

AP2/ERF family members are important in plant development in addition to coordinating abiotic stress response

The transcription factors belonging to the family AP2/ERF (APETALA2/ethylene response factor) have a characteristic AP2 DNA-binding domain [44]. The members of the AP2/ERF family can be further divided into five subfamilies based on their similarity for DNA binding domains: AP2, RAV, ERF, DREB, and ''others'' [45]. The AP2 subfamily is characterized by the presence of two AP2 DNA-binding domains and plays a key role in plant development [44] (Dietz *et al.*, 2010) whereas RAV subfamily members possess an AP2 domain and a B3 DNA binding domain and are involved in plant development as seen in *Arabidopsis*, but may also function in abiotic stress responses [46,47]. RAVL1, a RAV-like gene identified in rice, found to be involved in regulating brass inosteroid biosynthetic and signaling pathways [48].

DREB and ERF members bind to different DNA motifs

Although members of both the subfamilies DREB (dehydration-responsive element-binding protein) and ERF have a single AP2 DNA-binding domain but can be distinguished from each other on the basis of their specificities for DNA binding. DREB TFs interacts with DRE/CRT *Cis*-regulatory elements whereas ERF TFs interacts with GCC box *Cis*-regulatory elements present in the promoter of stress responsive genes [45,49]. The ERF proteins bind to GCC box *Cis*-element present in several pathogenesis related (PR) genes and plays an important role in disease resistance responses [50-52]. In *A. thaliana*, tobacco, and tomato have shown that over expression of ERF genes conferred resistance to fungal and bacterial pathogens [53]. ERF genes such as *CaPF1* (*Capsicum annuum* Pathogen and Freezing Tolerance Related Protein) [53], and *TaERF1* [54] responding to biotic and abiotic stress have also been identified in pepper and wheat respectively. Different benzothiadiazole induced ERF TFs such as OsBIERF1, OsBIERF2, OsBIERF3, and OsBIERF4 were analysed and it was found that among them OsBIERF1, OsBIERF3, and OsBIERF4 got induced in response to different to abiotic stresses like cold, drought, and salt stress as well as in biotic stress like pathogen infection [55]. In a study it was observed that the over expression of OsBIERF2 lead to an increase in stress tolerance against drought, high salinity, and low temperature [56].

DREB members are involved in drought, salt and cold responses, and mostly co-ordinate ABA-independent stress signaling pathway

DREB subfamily can be further categorized in two subclasses viz. DREB1/CBF and DREB2 based on their transcriptional

Table 1: List of transcription factors family involved in abiotic stress responses.
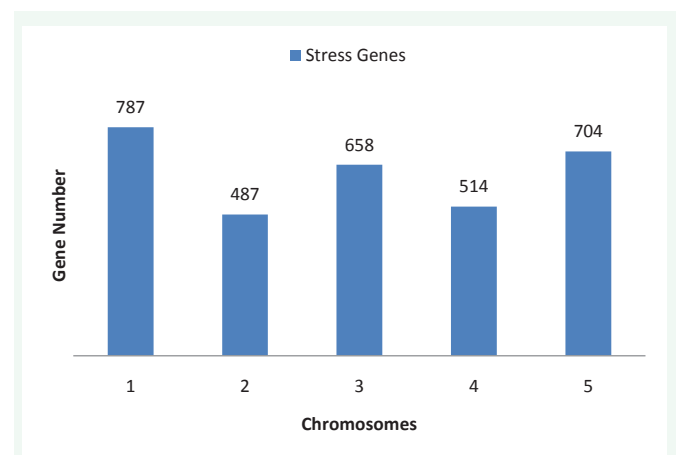
| S.no.	TF family	TF	*Cis*-acting elements to which TF binds	Sequence	Response	References
1.	AP2/ERF	OsBIERF1 OsBIERF3 OsBIERF4	GCC box	GCCCORE	Cold, drought and salt	Cao *et al.* 2006
		OsBIERF2	GCC box	GCCCORE	Drought, salt, low temperature	Oh *et al.* 2009
		DREB1A, DREB1B, DREB1C	DRE/CBF	A/GCCGAC	Cold	Agarwal *et al.* 2006; Nakashima *et al.* 2009
		DREB2A, DREB2B	DRE/CBF	A/GCCGAC	Drought, salt	Agarwal *et al.* 2006; Nakashima *et al.* 2009
2.	bHLH	AtAIB	E box	CANNTG	Drought	Rahie *et al.* 2010
		AtMYC2	E box	CANNTG	Drought	Abe *et al.* 2003
3.	bZIP	AREB1/ABF2, AREB2/ABF4, ABF3		ACGT	Drought	Fujita *et al.* 2005; Kang *et al.* 2002; Kim *et al.* 2004
4.	NAC	ANAC019, ANAC055, ANAC072	NACR	CATGTG	Drought, salinity, low temperature	Tran *et al.* 2004
		OsNAC6	NACR	CATGTG	Cold, salinity, drought	Ohnishi *et al.* (2005)
		TaNAC67	NACR	CATGTG	Drought, salt, freezing	Mao *et al.* (2014)
5.	WRKY	GmWRKY13	W-Box	TTGACC/T	Salt	Zhou *et al.* (2008)
		GmWRKY21, GmWRKY54	W-Box	TTGACC/T	Salt, drought	Zhou *et al.* (2008)
		WRKY25 WRKY26 WRKY33 WRKY39	W-Box	TTGACC/T	High temperature	Li *et al.* (2009, 2010, 2011)
6.	ARF/Aux-IAA	OsARF/OsIAA	AuxRE	TGTCTC	Cold, salt, drought	Jain *et al.* (2009)
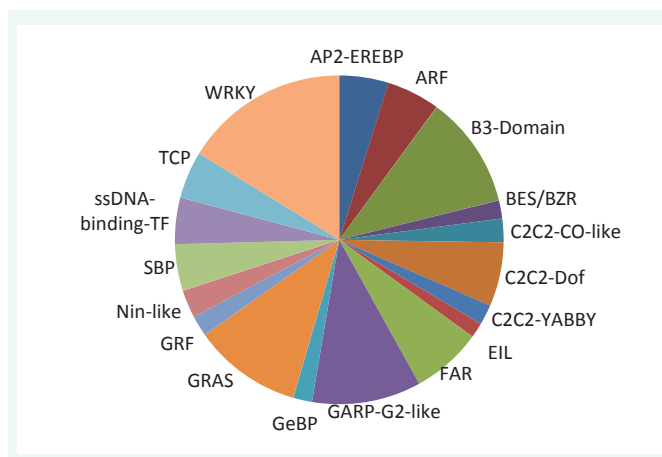
Figure 3 Major plant specific Transcription factors (Plant TFDB V3.0) (Jin et al. 2014) across the plant genomes.

their over expression produced similar tolerance phenotypes as produced by the over expression of DREB1A in *A. thaliana* [59,63]. Rice DREB2 genes, OsDREB2A and OsDREB2B, showed a similar response to drought and salt; OsDREB2B was also induced by cold, suggesting a putative role of DREB2 proteins in cold responses [65]. Over expression of DREB-binding transcription factor, VrDREB2A isolated from *Vigna radiate* [66] and HhDREB2 isolated from *Halimodendron halodendron*

response under abiotic stress [57,58]. The DREB1/CBF genes viz. DREB1A, DREB1B, DREB1C gets induced in response to cold stress only while DREB1D & DREB1F, were observed to respond under drought and salt stress, respectively. The DREB2 genes viz. DREB2A and DREB2B also gets induced in response to drought and high salt [57,59]. This indicates a crosstalk between DREB1/ CBF and DREB2 pathways in response to abiotic stresses [59-61]. The OsDREB1A and OsDREB1B genes showed differential expression in response to abiotic stress in rice [62-64] and

Figure 4 Distribution of stress-responsive genes on different chromosomes in *Arabidopsis thaliana* (STIFDB V2.0) (Naika *et al.* 2013; Shameer *et al.* 2009; Sundar *et al.* 2008)..

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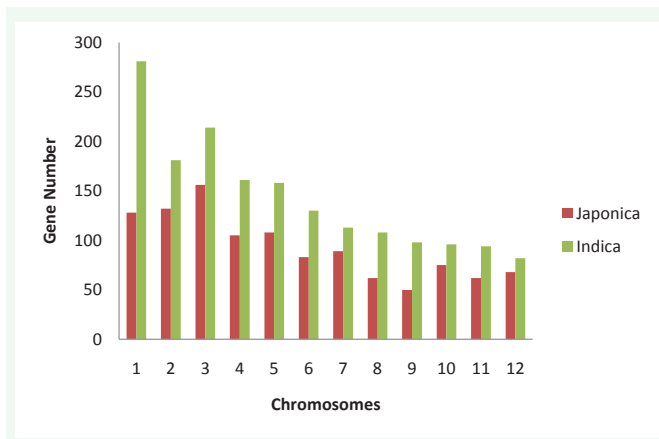
Figure 5 Distribution of stress-responsive genes on different chromosomes in *Oryza sativa* sub. *japonica* and *Oryza sativa* sub. *Indica* (STIFDB V2.0) (Naika *et al.* 2013; Shameer *et al.* 2009; Sundar *et al.* 2008).

conferred increased salt and drought tolerance in transgenic *Arabidopsis thaliana* [67]. Transgenic *Arabidopsis thaliana* over expressing the TF NnDREB2 isolated from lotus also exhibited elevated salt tolerance [68]. DREB2 proteins in barley, wheat, and maize found to be regulated at the post-transcriptional level by alternative splicing [59]; similar mode of regulation was observed in OsDREB2B [65]. Majority of the DREBs are involved in ABA independent stress responses; however, some studies have reported that DREBs are also responsive to ABA [58,60].

bHLH family

The basic/helix-loop-helix (bHLH) proteins are widespread among all living organisms from yeast to humans and constitute one of the largest transcription factor families. Members of the bHLH super family have signature domain of around 60 amino acids residues; highly conserved with two functionally distinct regions. The N-terminal end of the domain is the basic region, consists of 15 amino acids with high number of positively charged residues and is involved in DNA binding. The C-terminal end has the HLH region, functions as a dimerization domain. It consists of two α-helices separated by a loop region of variable sequence and length. The bHLH proteins recognize a DNA sequence motif (conserved consensus sequence) known as the E-box (5'-CANNTG-3') by conserved amino acids within the basic region of the protein and the nucleotides lying outside of E-box render binding specificity [69]. Depending on the identity of the two central bases, there are different types of E-boxes; most common among them is the palindromic G-box (5'-CACGTG-3'). At AIB, a bHLH3 homologue in *Arabidopsis* found to be involved in the induction of both drought and ABA- specific stress genes under stress conditions [70]. At MYC2 protein produced under drought stress in *Arabidopsis* acts as transcriptional activators enhancing the gene expressions of ABA-inducible genes [71]. Under cold stress, *Arabidopsis* expresses COR genes in order to survive low temperatures; two grapevine bHLHs have been found to modulate the expression of COR genes by acting as positive regulators [72]. Transgenic *Arabidopsis thaliana* carrying a grape bHLH transcription factor gene, *VvbHLH1* are more tolerant to drought and salt stresses [73]. It is reported that MYC3 and MYC4

bHLH TFs along with MYC2 acts as activators of Jasmonic acid (JA) responses [74]. Over expression **of TabHLH39** from wheat, in **Arabidopsis** significantly enhanced tolerance to salt, freezing stress and drought [75].

bZIP family members are also involved in light signaling and flower development

The bZIP transcription factors are characterized by the presence of a highly conserved bZIP domain; having two structural features (a) a basic region (16 amino acid long) having a nuclear localization signal followed by an amino acid stretch N-x7-R/K-x9 (b) a leucine zipper, consists of heptad repeats of Leu or bulky hydrophobic amino acids, such as Ile, Val, Phe or Met positioned exactly nine amino acids towards the C-terminus. The basic region helps in sequence-specific DNA binding whereas the leucine zipper region provides dimerization specificity. The bZIP proteins bind preferentially to an ACGT core of DNA sequences and the flanking nucleotides regulates their binding specificity [76].

The bZIP TFs have been found to be involved in abiotic stress signaling, light signaling [77], flower development [78] and pollen development [79]. Another study on rice genes [80] coding for bZIP TFs are being regulated at the level of transcription by auxins [81], gibberellins [82] and ethylene (in the form of ACC) [83]. This indicates that bZIP TFs mediates several signaling pathways. Yeast one-hybrid analysis of *Arabidopsis* cDNA libraries led to the identification of five similar bZIP proteins these are identified as AREBs or ABFs [84,85]. In *A. thaliana*, nine bZIP proteins belonging to the group-A bZIP family are classified as homologs of AREB/ABFs, and all have four conserved domains in addition to the bZIP domain.

Induction in AREB1/ABF2, AREB2/ABF4 and ABF3 TFs was observed in vegetative tissues in response to abiotic stresses, such as dehydration, salt stress and ABA [86] and a gain-of-function in mutant *A. thaliana* plants exhibited enhanced tolerance against drought stress [86-88].

Rice plants over expressing OsbZIPs showed more tolerance to high salinity and drought conditions, on the other hand knockout plants became sensitive to these stress conditions. Contrary to this, it was observed that over expression of OsABI5/OsbZIP10 made plants more sensitive towards salinity in comparison to those wild types plants [89]. A novel bZIP transcription factor, TabZIP60 from wheat when over expressed in *Arabidopsis* resulted in significantly improved tolerances to drought, salt, freezing stresses and increased plant sensitivity to ABA in seedling growth [90]. In almost all plants species, the bZIP-mediated signaling pathway is conserved. For example, bZIP TFs such as TRAB1 (TRANSCRIPTION FACTOR RESPONSIBLE FOR ABA REGULATION 1) in rice, HvABI5 (ABA INSENSITIVE 5) in barley, and ABI5 (ABA INSENSITIVE 5) in *Arabidopsis* are homologous to each other and acts in similar way to modulate ABA-dependent gene expression by interacting with their counterparts OsVP1 (rice VP1- VIVIPAROUS 1), HvVP1 (barley VP1), and AtABI3 (*Arabidopsis* ABA INSENSITIVE 3) respectively [91-93].

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NAC transcription factors also participate in stress and pathogen response

NAC TFs constitute one of the largest plant specific TF families having about 106 members in *Arabidopsis* and 149 members in rice [94,95]. NAC TFs have a conserved N-terminal domain which is a DNA-binding domain and a variable C-terminal domain [96-99]. These TFs are termed as NAC TFs, as derived from the three proteins: petunia NAM (No apical Meristem), and *Arabidopsis* ATAF-1 (*Arabidopsis* transcription activation factor 1) and CUC2 (cup-shaped cotyledon) having similar DNA-binding NAC domain [100,101]. As reported in *Arabidopsis*, NAC TFs bind to the *Cis*-element NACR (NAC recognition) with CATGTG motif [102].

Besides having role in plant development, the NAM, ATAF, and CUC proteins also participate in plant response to pathogens, viral infections and environmental stimuli [103-106]. NAC genes induced in respone to drought, salinity, and/or low temperature such as ANAC019, ANAC055, and ANAC072; when over expressed in transgenic *Arabidopsis* plants resulted into enhanced stress tolerance [102]. In rice, the transcription factor OsNAC6 gets induced in response to both biotic and abiotic stresses [107]. A novel **TaNAC8** protein has been identified in wheat which functions as a transcriptional activator to defense responses in both abiotic and biotic stresses [108]. Transgenic **Arabidopsis** plants over expressing **TaNAC67** experimentally showed enhanced tolerance to drought, salt and freezing stress [109]. *Arabidopsis* transgenic plants carrying genes CiNAC3 and CiNAC4 from *Caragana intermedia* encoding NAC TFs alter ABA sensitivity during seed germination and salt tolerance [110]. Over expression of GmNAC20 from *Glycine max* in *Arabidopsis* increases tolerance against salt and freezing stresses while the over expression of GmNAC11 improves salt tolerance [111]. Over expression of a maize stress-responsive NAC transcription factor, ZmNAC55 has been shown to increase drought resistance in transgenic *Arabidopsis* [112].

Enhanced tolerance against high temperature, drought, and oxidative stress was observed in rice over expressing TF SNAC3 [113] also over expression of MlNAC5 from *Miscanthus lutarioriparius* in *Arabidopsis* enhanced responses to salinity, drought and cold stresses [114]. Transgenic rice carrying a gene for TF named NAC67 from finger millet showed increased tolerance to drought and salinity [115]. In another case, tobacco plants carrying NAC1 gene from finger millet displayed increased tolerance to multiple stresses like oxidative, salinity and osmotic [116]. While overexpression of *NAC2* from *G. herbaceum,* showed enhanced drought tolerance in transgenic *Arabidopsis* and cotton [117]. Similarly, a NAC transcription factor JUNGBRUNNEN1 when over expressed in **Arabidopsis thaliana**, showed increase tolerance against heat stress [118].

WRKY family

WRKY TF family is one of the largest transcription factor families in plants as widely disturbed among all living organisms ranging from unicellular eukaryote *Giardia lamblia,* slime mold *Dictyostelium discoideum* to higher plants [119]. These TFs being an integral part of many signaling networks are involved in the regulation of many plant processes. WRKY proteins can either repress or activate important plant processes by acting

as repressor or activators. They are involved in signaling and transcriptional regulation via interactions with a variety of proteins, including MAP kinases, MAP kinase kinases, calmodulin, histone deacetylases, resistance proteins and other WRKY TFs. TFs belonging to the WRKY family have a characteristic DNA- binding WRKY domain of about 60 amino acid with invariant WRKY amino acid sequence at the N-terminus and an atypical zinc-finger structure at the C-terminus. The zinc-finger structure is either $CX_{4-5}CX_{22-23}HXH$ or $Cx_7Cx_{23}HxC$ [119-121]. WRKY transcription factors from *Glycine max viz.* GmWRKY13, GmWRKY21, and GmWRKY54 were found to be expressed differentially in response to various abiotic stresses [122]. This study suggested that in *Arabidopsis thaliana*, GmWRKY21 over expression led to cold tolerance, while GmWRKY54 over expression led to salt and drought tolerance. However, GmWRKY13 over expression enhanced salt and mannitol sensitivity, decreased ABA sensitivity and increased lateral roots. Transgenic *Arabidopsis* carrying a gene for WRKY TF, OsWRKY08 displayed enhanced tolerance to mannitol stress through increasing the lateral root number and primary root length during seeding root development [123]. Another WRKY transcription factor OsWRKY74, found to be involved in generating responses against cold stress in rice [124]. On the other hand, upon high temperatures some WRKY TFs such as WRKY25, WRKY26, WRKY33, and WRKY39 were found to be expressed in *A. thaliana* [125]. In plants **WRKY18**, **WRKY40** and **WRKY60** transcription factors play key roles in both biotic and abiotic stress responses and form a highly interacting regulatory network that modulates gene expression, stress responses and plant defense [126].

ARF family

Auxin plays an important role in certain processes in plant cell like growth and development. Auxin induces expression of several genes known as auxin response genes.

Which are grouped in three main catagories: auxin/indole-3-acetic acid (Aux/IAA), GH3 (Gretchen Hagen3), and small auxin-up RNA (SAUR) [127]. In promoters of various auxin-responsive genes many *Cis*-acting elements are occupied which are known as Auxin-responsive elements (AuxREs).

A family of transcription factor that bind to these AuxREs is Auxin response factors (ARFs). ARFs are encoded by a multi-gene family, consisting of more than 10 genes in *Arabidopsis thaliana*. ARF proteins contain a conserved DNA-binding domain, which identifies the special auxin-response elements (AuxREs) in the promoters of some genes viz. GH3, SAURs, and LBD for their activation or repression. The transcription of LBD genes is increased in response to exogenous auxin, indicating that the LBD gene family may act as a target of ARF [128]. Differential expression of auxin-responsive genes in rice has been shown in response to several abiotic stress viz. salt, drought and cold conditions, suggesting a crosstalk between auxin and abiotic stress signaling [129]. These three genes were also expressed in *Sorghum* along with another auxin responsive gene LBD (lateral organ boundaries). The results indicated an important role of auxin in salinity and drought stress response provides evidence for cross talk between auxin, brassinosteroid and abiotic stress signaling pathways [130]. Canonical Aux/IAA proteins share

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four characterized regions designated domain I, II, III and IV. Although the Aux/IAA transcription factor does not contain any DNA-binding domain but can coregulates the transcription of auxin-response genes cooperatively with ARF [131]. Aux/IAA, by binding to ARFs through conserved domains (domains III and IV), negatively regulate auxin-mediated transcription activity [132,133]. Several researches have shown that the interaction between ARF and Aux/IAA proteins mediates specific response to auxin. From the Yeast two-hybrid assays, cooperation between ARF and Aux/IAA, ARF5 or ARF7 with AtIAA1, 6, 12, 13, and 14 has been revealed [130]. AtIAA18 interacts with NPH4/ARF7 and ARF19 [134].

REGULONS OF ABIOTIC STRESS

Transcription factors (TFs) regulates gene expression by binding specifically to the *Cis*-acting elements located in the promoter region of the targeted genes. The expression of an array of genes can be controlled by a single TF; such kind of a transcriptional regulatory system is called a 'regulon'.

Different regulons have been identified in plants that are active in response to abiotic stresses

1. ABA-responsive element (ABRE) binding protein (AREB)/ABRE binding factor (ABF) regulon functions in ABA-dependent gene expression

2. Dehydration-responsive element binding protein 1 (DREB1)/C-repeat binding factor (CBF) and DREB2 regulons function in ABA-independent gene expression

3. NAC (or NAM, No Apical Meristem)/ZF-HD (Zinc Finger-Homeodomain) regulon

4. Myeloblastosis-Myelocytomatosis (MYB/MYC) regulon

5. Multi-protein bridging factor 1c (MBF1c) regulons

AREB/ABF and DRE/CRT regulons cross-talk

ABA is produced by plants in response to abiotic stress condition and plays an important role in regulation at molecular level [135]. The genes corresponding to high salinity and drought stress shows induction in response to ABA; as seen in *A. thaliana* and rice [15,136]. These ABA-dependent stress genes are regulated by AREB/ABFs [135,137]. AREB/ABFs TFs belong to the family of bZIP TFs as stated through yeast one-hybrid assay [84,85] (Uno *et al.* 2000; Choi *et al.* 2000). In *Arabidopsis*, 75 bZIP TFs have been identified, out of which 13 TFs are AREB/ABF and are kept under group A, which include members having four conserved domains [76,138]. ABA-responsive genes promoter region is characterized by the presence of a conserved *Cis*-element ABRE ((PyACGTGG/TC) required for their expression [139] and also ABA-responsive genes for their expression requires more than one ABRE or a combination of an ABRE and promoter requires a CE (coupling element) for proper functioning [135,137,140].For instance, two ABRE *Cis*-acting elements are required for the expression of *rd29B* in seeds and vegetative tissues of *Arabidopsis* [84,141] while ABRE along with coupling elements, CE1 and CE3 form the ABA-responsive complex which regulates wheat *HVA1* and *HVA22* genes [142]. Most CEs are found to be similar to ABREs, e.g. A/GCGT motif present in rice

[92]. In response to ABA, DRE/CRT sequence serves as a CE of ABRE suggesting that a cross-talk between ABRE/ABF and DRE/CRT regulons [141].

Presence of two ACGT elements in close vicinity in the promoter region is a feature of stress responsive genes and the co-occurrence of ACGT element across *A. thaliana*, rice, soybean and sorghum genomes indicates parallel evolution of ACGT elements from a common ancestral gene [143].

Activation AREB/ABF TFs requires ABA-mediated signals as reported in case of ABA-deficient *aba2* and ABA-insensitive *abi1* mutants, where the AREB/ABF TFs showed decreased while in case of ABA-hypersensitive *era1* mutants they showed enhanced activity [84]. Phosphorylation of AREB/ABF TFs by ABA-responsive 42-kDa SnRK2-type kinases (identified in *Arabidopsis* & Rice) was suggested as the probable mechanism of activation [84,144]. The Ser/Thr residues located in the R-X-X-S/T sites of AREB1 are phosphorylated by these kinases [145]. The phosphorylated AREB1 was able to express ABA-inducible genes even without ABA treatment when overexpressed in transgenic plants [145]. These studies suggest that AREB/ABFs are regulated by ABA-dependent phosphorylation of multiple sites within the conserved domain of AREB. ABFs get activated against different stresses for e.g. ABF1 in cold, ABF2 in salt, drought, heat and glucose; ABF3 in salt; ABF4 in cold, salt and drought [86,88], they also exhibit tissue specific expression. AREB/ABF regulons plays a key role in controlling ABA dependent signals generated in response to ABA, high salinity and dehydration as seen in *A. thaliana* and rice [86,146]. Only three AREB homologs (*AREB1/ABF2*, *AREB2/ABF4*, and *ABF*) have been identified in the **Arabidopsis** genome shows expression in response to ABA, drought, and high salinity in vegetative tissues, but not in seeds [86]. In contrast, during seed maturation *ABI5, AREB3, AtDPF2B and EEL* are expressed [138,147,148]. **Arabidopsis** TFS AREB2/ABF4 involved in ABA regulation shows homology to TFs TRAB1 from rice and HvABI5 from barely. Expression of **TRAB1** and **HvABI5** genes was detected in ABA-treated and drought-stressed seedlings, respectively [91,92,149]. Increased drought tolerance and ABA hypersensitivity was observed in transgenic *A. thaliana* plants overexpressing deleted and active forms of AREB1 [86]. Rice and soybean also show improved drought tolerance due to AREB1 over-expression [150,151]. ABA signaling pathways and AREB/ABFs in land plants, are found to be controlled by SnRK2, group A PP2Cs and RCAR/PYR/PYL ABA receptors [140,152,153]. It has been reported that for ABA-dependent signaling, the phosphorylation of AREB/ABFs by SnRK2s is crucial [154-156]. Studies reveal that group A PP2Cs evolved first in land plants and are involved in regulating the intrinsic desiccation tolerance as seen in the moss **Physcomitrella patens** [157].

DREB1/CBF and DREB2 regulons modulate ABA-independent gene expression

DREBs (Dehydration Responsive Element Binding proteins) are a type of AP2/ERF TFs found specifically in the plant kingdom. They have a conserved AP2/ERF motif. These bind to the ABA-independent DRE/CRT *Cis*-element having the core sequence A/GCCGAC [158-160]. The promoter regions of stress inducible

genes of several plants including A. thaliana and rice have been seen to carry these *Cis*-elements DRE/CRTs. Using Yeast one-hybrid screening, DREB1/CBF and DREB2 encoding cDNAs of *Arabidopsis* were purified [161,162].

In *Arabidopsis* two groups of DREB TFs: DREB1/CBF and DREB2 have been identified [162]. DREB1/CBF TFs in *A. thaliana* seen to be involved in the regulation of a wide variety of stress-responsive genes by interacting with DRE/CRT. Transgenic *A. thaliana* over-expressing DREB1/CBF TFs displayed improvements in tolerance to drought, salinity and freezing stresses, but growth defects were observed when expressed constitutively [162,163]. However, *A. thaliana* showed improved stress tolerance without any growth defects when DREB1 was over expressed under the control of the *A. thaliana* stress-responsive *rd29A* promoter [163].

A number of plant species such as wheat, rice, and maize, oilseed rape carry cold-inducible DREB1/CBF genes [163]. The expression levels of **DREB1/CBF** genes found to correlate with frost tolerance as QTLs (quantitative trait locus) for frost tolerance map to DREB1/CBF genes in *Arabidopsis,* diploid wheat (*T. monococcum)* and barley [164-167]. Thus, the function of the DREB1/CBF regulons is widely conserved in the regulation of cold stress responses. Transgenic crops such as chrysanthemum [168], and peanut [169] over-expressing DREB/CBF TFs depicted enhanced tolerance to drought. Apart from gene expression in response to cold, rice DREB1/CBF TFs seen to ameliorate to drought tolerance in transgenic rice [63]. OsDREB1A and OsDREB1B, rice DREB1/CBF-type genes shows induction in response to cold stress. Improved tolerance to drought, salinity and cold stress was observed in transgenic rice and *Arabidopsis* over-expressing OsDREB1 and DREB1 respectively, but under normal conditions growth was hindered. The transgenic rice also had increased levels of osmoprotectants (proline and soluble sugars). These results indicate that DREB1/CBF-type genes can be used for both monocot and dicot crop improvement against various abiotic stresses.

The second group of DREB TFs, the DREB2 gene to encode a DRE/CRT-binding protein in response to osmotic stress [162]. However, no relevant phenotypic changes were observed in transgenic plants over-expressing DREB2A reason found to be presence of a negative regulatory domain (NRD) in DREB2A, deleting this domain made DREB2A constitutively active (DREB2Aca) [60]. DREB2Aca over-expression resulted into up-regulation of stress-inducible genes [162] and also improved drought tolerance as seen in soybean and *Arabidopsis* [60,170]. Regulation of DREB2A protein stability requires NRD region of DREB2A. Conclusively, transgenic plants over-expressing DREB1A showed improved tolerance against freezing and dehydration stress while DREB2Aca over-expression provided tolerance against dehydration and to some extent against freezing stress. In DREB1A and DREB2A transgenic plants the expression of genes involved in carbohydrate metabolism was found to be different as indicated by microarray analysis data [171]. During dehydration and cold conditions, accumulation of different types of saccharides and sugar alcohols takes place in plants; as the expression of genes responsible for starch-degradation, sucrose metabolism and sugar alcohol synthesis changes actively. The

transgenic plants over-expressing DREB1A reported improved dehydration and freezing tolerance by increasing the level of metabolites in plants while on the other hand DREB2Aca over expression had no such effect on metabolite level. Also DREB2A is degraded by DRIPs, a C3HC4 RING domain containing protein which binds to DREB2A and mediate ubiquitination by acting as E3 ubiquitin ligase [64].

Enhanced thermo-tolerance was observed in transgenic plants overexpressing DREB2Aca, as it induces expression of heat shock stress related genes [60]. This observation indicates the role of DREB2s in both dehydration and heat shock stress responses. A variety of plants like barley, rice, maize, wheat and sunflower found to possess DREB2-type proteins [172]. GmDREB2A; 2 is a DREB2A ortholog has been isolated from soybean but the difference lies in the NRD sequence [172]. However GmDREB2A; 2 over-expression has different effects compared to DREB2A over-expression in transgenic plants. This indicates that over the course of time DREB2 regulons has underwent changes, but their basic functions remains the same in soybean and *Arabidopsis*. Genome wide analysis of maize revealed that natural variation in the promoter region of ZmDREB2.7 is responsible for drought tolerance in maize [173]. So, in order to improve drought tolerance in crops, DREB2 can acts as a potential candidate.

NAC/ZF-HD regulon

Transcription factor proteins such as NAM, ATAF and CUC are widely spread among plant species such as **Arabidopsis** and rice, having around 100 NAC genes [27]. NAC TFs play an important role in development and stress responses. SNAC genes encoded TFs recognize NACR (NAC recognition sequence; CACG core) and plays key role in improving tolerance against environmental stress [27]. Over-expression of stress-responsive *Arabidopsis* SNAC genes such as RD26 and ATAF1, and rice SNAC genes such as SNAC1, OsNAC6/SNAC2, and OsNAC5 can improve drought and/or high-salt stress tolerance [27,100,174-176]. Induced stress tolerance was observed in rice plants when stress-responsive NACs TFs binds to stress-responsive LIP9, OsNAC6, or OsHox24 promoters to up-regulate the expression of stress-responsive genes without having any negative effects on plant growth [27,175-177]. Over-expression of SNACs such as SNAC1 and OsNAC10 using root-specific promoter RCc3, lead to the enhancement of abiotic stress tolerance of rice in field conditions [178-180]. These studies state that tolerance for abiotic stress can be achieved by overexpressing SNACs using suitable promoters. Plants overexpressing drought-responsive factors experience growth defects; these defects can be overcome by controlling the expression of drought-responsive factors using drought-responsive or tissue/organ-specific promoters reported in roots and stomata [175,177].

ZF-HD TFs have a conserved ZF-domain containing several cysteine and histidine residues. The N-terminal is involved in protein-protein interaction while the C-terminal interacts with the DNA. These TFs were first identified in *Flaveria trinervia* using yeast one-hybrid screen [181] and bind to their cognate binding sites ZF-HDR having the core sequence CATGTG. 14 AtZF-HD genes have been identified in *Arabidopsis* having role in floral development [182]. AtZF-HD1 gets induced in response to salt and drought stress, and binds to its cognate recognition sequence in ERD1 promoter [29].

MYB/MYC regulon modulates ABA-dependent stress signaling

MYB/MYC regulon participates in ABA-dependent stress signaling. Elevated levels of ABA causes accumulation of MYB and MYC TFs. MYB TFs like AtMYB4, AtMYB6, AtMYB7, AtMYB44, AtMYB73, AtMYB77 and AtMYBCDC5 shows constitutive expression in all plant tissues/organs under different stress conditions [183]. During dehydration and ABA-induction studies, *Rd22* was found to be expressed by the cooperative function of AtMYB2 and AtMYC2 that act as transcriptional activators [71,184]. AtMYB102 is thought to club dehydration, osmotic or salinity stress, ABA application, and wound signaling pathways [185]. The light-induced opening and dark-induced closing of stomata reported to be controlled by AtMYB60 and AtMYB61 respectively [186,187]. AtMYB44, AtMYB73, and AtMYB77 shows activation in response to wounding [188], white-light [189], cold stress [15], and salt stress [190]. Mutants like *fus3* (fusca3), *lec1* (leafy cotyledon1) and *abi3* (ABA-insensitive3) show a reduced AtMYB44 and AtMYB77 expression [191]. AtMYB44 acts in an ABA-independent manner and imparts abiotic stress tolerance by enhancing stomatal closure [192]. AtMYB15 negatively regulates freezing tolerance, while it is up regulated during cold and salt stress in both vegetative and reproductive tissues [27] (Agarwal *et al.* 2006). Salinity, drought, cold and ABA were shown to regulate the transcription of AtMYB41 in *Arabidopsis* [193].

Under abiotic stress conditions, the expression of GmMYB76, GmMYB92 and GmMYB177 gets induced. Over expression of these TFs in *A. thaliana* showed improved stress tolerance to salt and freezing [194]. Also in case of rice, *Arabidopsis*, maize and soybean MYB TFs have been found to control a variety of cellular processes like cell cycle and cell morphogenesis [195-197]. In rice, MYB53 protein show induction in response to cold and salt, while gets repressed against ABA response. Over expression and RNA interference studies have confirmed the role of MYB53 in cold responses. *Arabidopsis* over-expressing OsMYB3R-2 showed increased tolerance against cold stress [198]. OsMYB3R-2 regulates cell cycle progression during cold stress by targeting cyclin genes involved in G2/M transition [199]. Varying levels of tolerance were observed in different plant species overexpressing OsMYB4 [21]. OsMYB4 overexpressed in *Arabidopsis* transgenic plants showed enhanced tolerance against cold, drought and against biotic stress [200,201] (Mattana *et al.* 2005; Vannini *et al.* 2004). In transgenic tomato plants OsMYB4 overexpression resulted into an increased tolerance against drought and biotic stress [201], while enhanced drought and cold tolerance was observed in transgenic apple plants [202]. These studies clearly points that OsMYB4 over expression resulted into enhanced drought tolerance in all plants.

MBF1c regulon coordinates the heat stress response

Heat stress response in plants is a highly conserved process. It may be acquired or basal thermo tolerance [203] and is coordinated by at least two key components, Heat shock factors (HSFs) and the Multi-protein bridging factor 1c (MBF1c) proteins [204]. HSFs function as DNA-binding transcriptional regulators that control heat shock response by binding to defined heat shock response elements (HSEs). Pathways involving ethylene, salicylic acid and trehalose, have also been shown to play a role in thermotolerance in plants [205].

MBF1c has been identified as a key regulator of thermotolerance in plants and its mechanism is still unknown [204]. MBF1 is a highly conserved protein that is thought to function as transcriptional co-activator. CTAGA has been identified as its putative response element. In *A. thaliana*, MBF1 is encoded by three different genes (*Mbf1a, b, c*). MBF1a (At2g42680) and MBF1b (At3g58680) are developmentally regulated [206], MBF1c (At3g24500) plays a role in thermotolerance [204]. It acts upstream of salicylic acid, ethylene, and trehalose signaling during heat stress [204,207]. It binds to heat-inducible TPS5 (trehalose phosphate synthase 5) protein, and gets localized to the nucleus during heat stress [204] (Suzuki *et al.* 2008). Mutants of TPS5 were found to be thermo-sensitive, suggesting the presence of a heat stress response network, with MBF1c as a key regulator. In *Arabidopsis*, MBF1c is elevated in response to pathogen specificity, salinity, drought, heat, hydrogen peroxidase and application of ABA & SA [206,208,209]. MBF1c controls a regulon of 36 different transcripts during heat stress, including DREB2A, two HSFs and several ZF proteins [59]. Constitutive expression of MBF1c in soybean enhances yield production in plants grown under controlled growth conditions without causing adverse effects on growth [59].

BIOINFORMATICS TOOLS TO UNDERSTAND THE TRANSCRIPTION REGULATORY NETWORK

In cell gene transcription is basically controlled by transcription factors that bind to the sites located upstream of the gene coding sequence like promoter and enhancer regions. A comprehensive knowledge about the regulatory mechanism of genes networks present in the cell is prerequisite for characterizing complex biological processes. Genes which are expressed in the same tissue under similar conditions mostly show some similar organization of at least some of these regulatory binding elements. In this way the arrangement of promoter motifs acts as an impression of the transcriptional regulatory mechanisms in a specific biologic background and in this waygive information about signal and tissue specific control of expression. Analysis of promoters for organizational charactersticshas its own importance which acts as a connection between the nucleotide sequence of the genome and the dynamic aspects of gene regulation and expression. Network component analysis (NCA) [210], Computer modeling of promoter organization a tool to study transcriptional coregulation [211], PAINT (Promoter Analysis and Interaction Network Generation Tool) [212] for gene regulatory network identification are some bioinformatics tools available which can be used to study complex transcription regulatory networks.

DISCUSSION AND FUTURE PROSPECTS

Plants have evolved to cope up with a continuum of environmental conditions ranging from the most favorable to the most hostile. They respond accordingly in the most convenient manner with the help of network of CREs and TFs that modulate the expression of suitable genes. Deciphering the operational network of CREs and TFs will give us a comprehensive knowledge of the regulatory circuits allowing us to design plants better

suited to meet the challenges of growing food demand and global climate change. This review is an attempt to provide an insight into the intricate web of TFs and CREs involved in various abiotic stress responses.

Transcriptional regulation is a result of fine-tuned communication between different *Cis*-regulatory elements to which different TFs or co-TFs bind. From a limited pool of TFs and promoter architecture, a single TF can elicit several biological responses by interaction with other TFs or co-TFs [57]. The ABA-dependent stress pathway gets activated through different ABREs, MYCRs and MYBRs whereas ABA-independent pathway is activated through DREB TFs.

The CREs and TFs play an important role in transcriptional regulation by acting as molecular switches and regulating the dynamic network of stress-responsive genes. Transcription Factors such as DREB1/CBF, DREB2, AREB/ABF and NAC cross-talk during abiotic stress response, such as drought, cold and heat. These factors can be used to enhance drought tolerance in a variety of crops. In fact, many groups have used these TFs for improved drought tolerance [213,214] in crops like, wheat [215,216], peanut [169], potato [217,218], hot pepper [168] and soybean [170,219,220]. Stress-specific over-expression of DREB1A in plants like rice and peanut has improved drought tolerance and grain yield [170,213]. These results indicate the possibility of improving stress tolerance by over-expressing key TFs under the control of suitable promoters, despite the complexity of regulatory network during osmotic stress in plants.

The aim of *Cis*-engineering of plants is to achieve multiple stress tolerance with increased productivity. However, the technique is still in nascent stages. Transcriptomics and proteomics help in the identification and characterization of stress-responsive TFs and co-TFs. Systems biology has helped to decipher their regulatory networks and cross-talk during abiotic stress responses. As a result, potential TF candidates have been identified for multiple stress tolerance. However, only a few have been functionally characterized in the plant genome. Therefore, there is a need to understand the convergence points between different *Cis*-regulatory elements and TFs within the regulon as well as between different regulons. This understanding of the transcriptional cross-talk between regulons will help in designing better stress tolerant plants.

Attempts to improve drought tolerance using TFs like DREB1/CBF, AREB/ABF and NAC TFs, in various crops including rice, wheat and soybean, showed that the over-expression of these TFs had an effect on other signaling pathways. Besides, the trans gene expression was found to be dependent on the genetic background of the host species as well as the environmental conditions.

To develop stress tolerant crop varieties, stress responsive TFs could be used as candidate genes as allele mining in breeding programmes or as marker assisted selection (MAS) [177].

With the advancement in Omics technologies, plethora of data is being generated every day. Gene discovery and functional genomics are at its peak now. Attempts are being made to fit data obtained by omics technologies into functional networks and molecular hubs are being deciphered on a regular basis which

helps us in understanding of biological processes at physiological and cellular level [221]. With the advancement of omics technologies it has been identified that 10% of *Arabidopsis* genes are sugar responsive, suggesting that in abiotic stresses, sugar has greater role to play [222]. A phosphoproteomic analysis of the response of maize leaves to drought, heat and their combination stress showed that heat, drought and the combination stress significantly changed the phosphorylation levels of 172,149 and 144 phosphopeptides respectively and globally which corresponds to 282 proteins [223]. Functional characterization using phosphoproteins and otherwise hasledto identification of new pathways for enhancement of crop stress tolerance.

The purpose of this review was to explore past and more recent researches that have focused on cross talk between *Cis*-regulatory elements and their corresponding TFs. Deciphering the operational network of CREs and TFs will give us a comprehensive knowledge of the regulatory circuits allowing us to generate plants that can combat various abiotic stresses and ultimately to meet the challenges of growing food demand and global climate change.

Over expression of certain TFs may affect the equilibrium among the various TFs in the network and affect their cross-talk. Therefore, the molecular effects of TF over expression should be studied in addition to the stress tolerance assays. Besides, most of the TF over expression studies have targeted a particular stress condition. The need of the hour is to study multiple potential stress-responsive TFs, and focus on multiple stress tolerance along with increased productivity.

Over expression studies have been done mainly on model plants. These studies should be extended to other plants, including different cultivars. It is necessary to monitor the effects of TF over expression in a variety of genotypes and environments.

Reproductive failure has been reported during stress conditions. However, the studies focus mainly on the developmental stages rather than the flowering stages. Therefore, efforts should also focus on reproductive success of the plant.

Finally, the main aim of all these efforts is to increase productivity. Over expression of certain TFs is bound to affect other physiological processes of the plant. Therefore, efforts should be made to study maximum plant parameters for any adverse effect. The real potential of these TFs can be judged only after they pass the test of field trials.

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